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Seminars article

Update of systemic immunotherapy for advanced urothelial carcinoma

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Abstract

Purpose: Until recently, therapeutic options for metastatic urothelial carcinoma (UC) were limited to cytotoxic chemotherapy. Cisplatin-based combination chemotherapy has proven benefit in the perioperative settings for muscle-invasive disease and for metastatic disease. A large proportion of patients is cisplatin-ineligible and limited to less effective chemotherapeutic options. However, treatment options have recently expanded with the development of systemic immunotherapy with checkpoint inhibitors (CPIs).Herein we review the clinical trial data supporting the use of CPIs in UC. We also describe ongoing clinical trials that are exploring CPIs in novel combinations and in a variety of disease settings.

Methods: A comprehensive literature review was performed using Medline/Pubmed and clinical trials.

Results/Conclusions: Based on results of the IMvigor 210 clinical trial, the anti-programmed death-ligand1 antibody atezolizumab gained regulatory approval in May 2016 for use in locally advanced and metastatic UC in patients with progression of disease despite prior platinum-based chemotherapy. Since that time, additional CPIs (avelumab, durvalumab, nivolumab, and pembrolizumab) have gained regulatory approval in the postplatinum setting. The approval of pembrolizumab was supported by KEYNOTE-045, the first reported randomized, phase III trial of a CPI in UC. Atezolizumab and pembrolizumab are also approved for first-line therapy for cisplatin-ineligible patients with locally advanced or metastatic disease. The rapid expansion of therapeutic options in UC has shifted the treatment paradigm.

Keywords: Immunotherapy; Checkpoint inhibitors; Urothelial carcinoma

Introduction

Following the development of first-line cisplatin-containing combination chemotherapy, there had been no significant advances in the treatment of metastatic urothelial carcinoma (UC) over several decades [1]. However, the median survival with cisplatin-based chemotherapy was only 12 to 15 months. Moreover, cisplatin-ineligiblity is frequent as defined by renal dysfunction, Eastern Cooperative Oncology Group (ECOG)-Performance status (PS) = 2 or comorbidities (cardiac dysfunction, neuropathy, and hearing loss) [2]. Cisplatin-inelgible patients exhibit a dismal median survival of 8 to 9 months with carboplatin-based combination chemotherapy [3]. Salvage chemotherapy with taxanes and vinflunine yields dismal median survivals of 6 to 8 months [4–6]. The therapeutic landscape has dramatically changed since 2016. The arrival of Immunotherapy with checkpoint inhibitors (CPIs) has revolutionized the treatment of advanced UC [7].

Historically, immunotherapy with intravesical Bacille Calmette-Guerin (BCG) has reduced recurrences in non-muscle invasive bladder cancer (NMIBC) [8]. BCG was initially approved by the FDA in 1990 establishing a role for immunotherapy in UC. In muscle-invasive bladder cancer (MIBC), the extent of tumor-infiltrating CD8+ lymphocytes was reported to be associated with recurrence free and overall survival [9]. Given the established role of immunotherapy in NMIBC and the prognostic significance of TILs in MIBC, there was a strong rationale for evaluating CPIs in UC.

Regulatory approval of multiple programmed death (PD) 1 and PD-ligand (L)1 inhibiting CPIs for advanced UC since May 2016 has ushered in a new era. At this time, there are 3 anti-PD-L1 inhibiting monoclonal antibodies (atezolizumab, avelumab, and durvalumab) and 2 anti-PD-1

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Table 1
Results from trials evaluating CPIs in UC

Trial	Agent	Phase (*n*)	Population	ORR, %	Median OS, mo	trAEs, %
First line (platinum naïve)						
IMvigor 210 cohort 1 [16]	Atezo	II (119)	LA or M, plat-naive	23	15.9	G3-4: 16
KEYNOTE-052 [24]	Pembro	II (370)	LA or M, plat-naive	29	NR	G3-4: 18
Second line (postplatinum)						
IMvigor 210 cohort 2 [17]	Atezo	II (310)	LA or M, post-plat	15	7.9	G3-4: 16
KEYNOTE-045 [21]	Pembro vs. Chemo	III (542)	LA or M, postplat	P: 21.1 C: 11.4 (P = 0.001)	P: 10.3 C: 7.4 (HR = 0.73; P = 0.002)	Any: P (60.9) C(90.2) G3–4: P (15) C (49.4) G5: P (1.5) C (1.5)
CheckMate 275 [14]	Nivo	II (270)	LA or M, postplat	19.6	8.74	G3–4: 18
CheckMate 032 [30]	N3I1 (104) Vs. N1I 3 (26) Vs Nivo (78)	I/II	LA or M, postplat	26.0 38.5 25.6	NR	G3–4: 31.7 G3–4: 30.3 G3–4: 23.1
NCT01693562 [25]	Durvalumab	I/II (191)	LA or M, postplat	17.8	NR	G3–4: 6.8
JAVELIN [28]	Avelumab	Ib	LA or M, postplat	17.4	7.4	G3–4: 8.4

Atezolizumab chemo (C) = chemotherapy; G = grade; Ipi (I) = ipilimumab; LA = locally advanced; M = metastatic; Nivo = Nivolumab.

inhibiting antibodies (nivolumab and pembrolizumab) with regulatory approval for UC. In this review, we will discuss the clinical trial data supporting the use of CPIs in UC (Table 1) and ongoing clinical trials of immunotherapy in UC (Table 2).

Checkpoint molecules

A brief overview of checkpoint molecules is warranted (Fig.). Checkpoint molecules inhibit T-cell mediated damage of healthy tissues. However, inhibitory signals from checkpoint molecules may allow cancers to evade immune surveillance [10]. PD1 is expressed on T-cells and PD-L1 is expressed on immune and cancer cells. The interaction between PD-1 and PD-L1 inhibits distal T-cell function within the tumor microenvironment and leads to exhaustion of competent cytotoxic T-cells. By targeting either PD-1 or PD-L1 this inhibitory signal can be overcome allowing for a more effective immune response to cancer [11,12]. Similarly, cytotoxic T-lymphocyte antigen (CTLA)-4 is expressed on T-regulatory cells (Tregs), which inhibit cytoxic T-cells mostly at the time of early T-cell priming within lymph nodes [12].

In addition to PD1/PD-L1 and CTLA-4, which are targeted by currently commercially available agents, an expanding list of other coactivating and co-inhibiting T-cell

Table 2
Ongoing randomized studies evaluating CPIs in UC

NCT identifier trial name	Treatment arms	Phase	Population	Primary endpoint
NCT02516241 DANUBE	(1) Durval+ Treme (2) Durval (3) Gem + Plat	III	Stage IV, first line	PFS and OS
NCT02807636 IMvigor 130	(1) Gem + Plat + Atezo (2) Gem + Plat + Placebo	III	LA or M, first line	PFS and OS
NCT02853305 KEYNOTE-361	(1) Pembro (2) Gem + Plat + Pembro	III	LA or M (bladder, urerthra or upper tract), first line	PFS and OS
NCT03036098 CheckMate 901	(1) Nivo + Ipi (2) Gem + Plat	III	LA or M, first line	PFS and OS
NCT02603432 JAVELIN Bladder 100	(1) Avelumab (2) BSC	III	Maintenance	OS
NCT02500121 HCRN GU14–182	(1) Pembro (2) Placebo	RPII	Maintenance	6 mo PFS
NCT02302807 IMVigor 211	(3) Atezo (4) Chemo	III	LA or M, postplatinum	OS: Did not meet endpoint [19]
NCT02450331 IMvigor 010	(1) Atezo (2) Observation	III	Adjuvant	DFS
NCT02632409 CheckMate 274	(1) Nivol (2) Placebo	III	Adjuvant	DFS

Atezo = Atezolizumab; Avel = Avelumab; BSC = best supportive care; chemo = chemotherapy; DFS = disease-free survival; Durva = Durvalumab; Gem = Gemcitabine; LA = locally advanced; M = metastatic; Nivo = Nivolumab; OS = median overall survival; Pembro = Pembrolizumab; Plat = platinum; RPII = randomized phase II; Treme = Tremelimumab.